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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,063	06/22/2005	Peter Geigenberger	13311-00008-US	4909

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EXAMINER	
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ART UNIT	PAPER NUMBER
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,063	GEIGENBERGER ET AL.	
	Examiner	Art Unit	
	Brendan O. Baggot	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45 and 47-58* is/are pending in the application.

4a) Of the above claim(s) _ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45 and 47-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

1. The text of those sections of title 35 U.S.C. not included in this action can be found in a prior Office action.

2. Any rejection or objection not repeated herein is withdrawn.

3. The objections to the claims for reciting non-elected sequences are hereby withdrawn in light of applicant's amendments.

4. The rejections under 102(b) and (e) are withdrawn in light of Applicant's amendments.

5. The Office acknowledges the receipt of Applicant's Response filed 7/27/07. Claims 47-58 are newly added. Claims 45, 47-58 are pending and examined.

Claim Objections

6. Claims 54, 56-57 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are directed to product claims but depend from a method claim. See MPEP § 608.01

Claim Rejections - 35 U.S.C. §112, second paragraph

7. Claims 47-48 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

This rejection is maintained for reasons of record set forth in the Official action mailed 9/8/06. Applicant's arguments filed 7/27/07 have been fully considered but are deemed not persuasive.

This rejection has been modified in light of Applicant's amendments.

In Claims 47-48, it is unclear what is being retained in the "derived" hemoglobin from *inter alia, Arabidopsis thaliana*. It is unclear what the structure of the derived product is or what the derivation is. Clarification and/or correction are required.

Applicant traverses the previous rejections made under 112.2 arguing primarily that the amended claims obviate the rejections.

This is not persuasive because the claims as amended are rejected for the reasons set forth above.

Claim Rejections - 35 U.S.C. §112, first paragraph, enablement

8. Claim 51 is rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for SEQ ID NO: 5 or a sequence encoding SEQ ID NO: 6, and a method for producing same, does not reasonably provide enablement for sequences having less than 100% sequence identity to SEQ ID NO: 5 and 6. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record set forth in the Official action mailed 9/8/06. Applicant's arguments filed 7/27/07 have been fully considered but are deemed not persuasive.

The claims are broadly drawn to any sequences with at least 90% sequence identity to SEQ ID NO: 5.

Applicants teach only SEQ ID NO: 5 and SEQ ID NO: 6.

Applicants do not teach sequences with at least 90% sequence identity to SEQ ID NO: 5 having the enzymatic activity of SEQ ID NO: 6.

The claims are broadly drawn to any sequence having at least 90% nucleic acid sequence identity to SEQ ID NO: 5. The claims are also drawn to any hemoglobin, and encompass any sequences with as little as 90% sequence identity to SEQ ID NO: 5. The broad language expressly includes mutants and allelic variants, including mutations knocking out the active site and the allosteric regulatory sites. The specification does not enable any person skilled in the art to which it pertains, or with which it is most reasonably connected, to practice the invention commensurate in scope with these claims.

Claims reciting less than 100% sequence identity are not enabled because they encompass unspecified base substitutions, deletions, additions, and combinations thereof while retaining the ability to bind oxygen. Neither the state of the prior art nor the Applicant teaches what region(s) of SEQ ID NO: 5 or 6 must be retained for catalytic activity. The claims encompass inoperable embodiments but the specification provides no guidance as to how such inoperable embodiments

can be readily eliminated without undue experimentation. Moreover, while one skilled in the art can readily make mutations to SEQ ID NO: 5 or the sequence encoding SEQ ID NO: 6, further guidance is needed as to what mutations would not ablate enzymatic activity. Applicant provided no working example of any mutant sequences within the less than 100% sequence identity scope which has the asserted activity. Accordingly, the claimed invention cannot be practiced without undue experimentation commensurate in scope with the claims.

It is well established that sequence similarity is not sufficient to determine functionality of a coding sequence. See the teachings of Doerks (TIG 14, no. 6: 248-250, June 1998), where it states that computer analysis of genome sequences is flawed, and "overpredictions are common because the highest scoring database protein does not necessarily share the same or even similar functions" (the last sentence of the first paragraph of page 2484. Doerks also teaches homologs that did not have the same catalytic activity because active site residues were not conserved (page 248, the first sentence of the last paragraph).

Lazar et al (1988, Mol. Cell Biol. 8:1247-1252) teach that a replacement of aspartic acid at position 47 with an alanine or asparagine in transforming growth factor alpha had no effect, but that a replacement with serine or glutamic acid sharply reduced biological activity (see the abstract). Small changes in amino acid sequence can even completely modify enzymatic function. Broun et al (1988, Science 282:1315-1317) teach that a change of four amino acids converts an oleate 12-desaturase to a hydroxylase. Thus Lazaar et al and Broun et al demonstrate that one or a few amino acid substitutions could dramatically affect the biological activity and the structure-function characteristics of a protein.

While Applicant is not required to provide working examples of each claimed embodiment, further guidance as to which region of the disclosed sequences can tolerate mutations while retaining activity is required. Absent such guidance, one skilled in the art would not be able to use the claimed nucleic acid sequences without undue experimentation.

Applicant traverses that the claims are now directed to method claims.

This is not persuasive because a process is not enabled unless all the reagents required to practice the invention are also enabled.

Applicant traverses that by way of working examples, the specification of the present application demonstrates how to generate expression constructs for tissue-specific expression (Example 5 at pages 19-20), plant transformation (Examples 6 and 7 at pages 20-23), analysis of hemoglobin expression in transformed plant (Example 8 at pages 23-25), and analysis of the effect of the hemoglobin expression on the production of the desired product (Examples 9- 11 at pages 25-30).

This is not persuasive because the rejection is not over the constructs per se, the plant transformation method per se, or expression analysis methods per se. The rejection is drawn to sequences which are at least 90% sequence identical to SEQ ID NO: 5.

Applicant traverses that only routine experimentation would be required for one of ordinary skill in the art to follow the teaching of the present application and to produce a transgenic plant expressing a hemoglobin having at least 90% identity with Seq ID No: 5 and to recover the starch and/or oil produced from such a transgenic plant.

This is not persuasive because not only does the claim not require any specified activity, there is a large number of sequence variations encompasses by the claims. The percent identity

language encompasses such a large number of sequence variations, that it would be undue experimentation to test them all to prove functionality. Given the approximately 48 different positions and the 4 different possible nucleotides at each position, the number of different sequences is $48^4 = 480,000$ different sequences that would need to be transformed into plants and function demonstrated in plants.

Applicant traverses that only routine experimentation would be required to one skilled in the art to determine whether a hemoglobin-coding sequence with at least 90% identity with the sequence of SEQ ID NO: 5 has the desired activity.

This is not persuasive because Claims reciting less than 100% sequence identity are not enabled because they encompass unspecified base substitutions, deletions, additions, and combinations thereof while retaining the ability to bind oxygen. Neither the state of the prior art nor the Applicant teaches what region(s) of SEQ ID NO: 5 or 6 must be retained for hemoglobin activity. The claims encompass inoperable embodiments but the specification provides no guidance as to how such inoperable embodiments can be readily eliminated without undue experimentation. Moreover, while one skilled in the art can readily make changes to SEQ ID NO: 5 or the sequence encoding SEQ ID NO: 6, further guidance is needed as to what mutations would not ablate hemoglobin activity. Applicant provided no working example of any mutant sequences within the less than 100% sequence identity scope which has the asserted activity. Accordingly, the claimed invention cannot be practiced without undue experimentation commensurate in scope with the claims.

Claim Rejections - 35 U.S.C. §112, first paragraph, written description

9. Claim 51 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record set forth in the Official action mailed 9/8/06. Applicant's arguments filed 7/27/07 have been fully considered but are deemed not persuasive.

The claim reciting at least 90% sequence identity lacks adequate written description because Applicant does not disclose a representative number of species as encompassed by these claims. The claims encompass mutants and allelic variants, yet no structural variant has been disclosed, nor are any known to exist in the art. The claim also encompasses hemoglobin polypeptides from other species. The implication is that there is a gene and a protein other than that disclosed which exists in nature, but the structure thereof is not known. Thus, there are insufficient relevant identifying characteristics to allow one skilled in the art to predictably determine such mutants, allelic variants and hemoglobin polypeptides from other plants and organisms that have 90% identity to Seq ID No 5, absent further guidance.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that a written description of an invention "requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court also concluded that

"naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id. Further, the court held that to adequately describe a claimed genus, Patent Owner must describe a representative number of the species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus." Id.

Finally, the court held:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. Id.

See also MPEP Section 2163, page 174 of Chapter 2100 of the August 2005 version, column 1, bottom paragraph, where it is taught that

> [T]he claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

See also Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ 2d 1016 at 1021, (Fed. Cir. 1991) where it is taught that a gene is not reduced to practice until the inventor can define it by "its physical or chemical properties" (e.g. a DNA sequence).

Given the claim breadth and lack of written description as discussed above, the specification fails to provide an adequate written description of the genus of sequences as broadly claimed. Given the lack of written description of the claimed genus, any method of

using the claimed genus would also be inadequately described. Given the lack of written description of the claimed method, any products therefrom would also be inadequately described.

Accordingly, one skilled in the art would not have recognized Applicant to have been in possession of the claimed invention at the time of filing. *See* The Written Description Requirement guidelines published in Federal Register/ Vol. 66, No. 4/ Friday January 5, 2001/ Notices: pp. 1099-1111.

Applicant traverses that the amended claim 45 complies with the written description requirement.

This is not persuasive because for the reasons set forth above.

Claim Rejections - 35 U.S.C. §103

10. Claims 45, 47-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harper (PGPUB - 2002/0160378-US, published 10/31/02) in view of Nykiforuk (6552250-US, issued 4/22/03) and further in view of Sowa (1998) PNAS 95: 10317-10321).

This rejection is modified in light of Applicant's amendments and maintained for reasons of record set forth in the Official action mailed 9/8/06. Applicant's arguments filed 7/27/07 have been fully considered but are deemed not persuasive.

Applicant's traversals to Arntzen and Trevaskis are moot in light of the modification of the rejection as necessitated by amendment.

The claims are drawn to methods of transforming plants with hemoglobin – SEQ ID NO: 5 – and monocot and dicot plants therefrom.

Harper teaches a method (paragraphs 166, 164, Claim 29) for the production of starch and/or oil comprising growing a transformed plant (*See* paragraph 137, 164) that expresses at least one hemoglobin and recovering the starch and/or oil from said transformed plant, wherein the hemoglobin is derived from *Arabidopsis thaliana* (See paragraph 11), wherein the hemoglobin is expressed in a storage-organ- specific manner (See paragraph 99), wherein the hemoglobin is expressed in a tuber-specific manner (See paragraph 99, 155 (potato)), wherein the hemoglobin is encoded by the nucleotide sequence as set forth in SEQ ID NO: 5 (See paragraph 60; Table 1, p. 45, SEQ ID NO: 1274 (a 100% match); Table 1, p. 47, SEQ ID NO: 1539 (a 100% match)), wherein the transformed plant is rice (See paragraphs 155, 56, 160), soybean or potato (See paragraphs 155, 56, 160). (See also paragraph 155; Claims 29, 52, 56, 57).

Harper does not teach recovering the starch and or oil.

Nykiforuk teaches recovering oil from a plant. (6552250-US, issued 4/22/03, see claim 5).

Sowa teaches a method for the production of a transformed plant expressing hemoglobin from barley and growing said plant. (see Figure 2, p. 10318 generally, and p. 10318, left col., 2nd para.) Sowa also teaches corn which produces starch and oil. Sowa also teaches that hemoglobins function to maintain energy status of cells under high energy demand. (see p. 10317 right col., 1st para.).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to express Harper's *Arabidopsis thaliana* hemoglobin of SEQ ID NO: 5 in light of Sowa's barley hemoglobin expression for the purposes of optimizing genetic elements to improve expression levels of the gene of interest or for the purpose of producing hemoglobin in alternate host systems such as other plants. Barring unexpected results, any hemoglobin

sequence known in the art can be expressed without any surprising or unexpected result. Expression of hemoglobin in different plant hosts, including in both monocots and dicots have been successful as evidenced by Sowa. Nykiforuk teaches the step of recovering oil.

One skilled in the art would have been motivated to generate the claimed invention because Sowa teaches that the generation of protein and oil are high energy demand activities which could benefit from the expression of hemoglobins. (Sowa, p. 10317, right column, first paragraph, last sentence). One would have done so with a reasonable expectation of success because Sowa was successful in expressing the barley hemoglobin and because corn starch and corn oil are routinely recovered from mature corn. Accordingly, one of ordinary skill in the art would have generated the claimed invention.

100% identical to SEQ ID NO: 5 anticipates at least 90% identical to SEQ ID NO: 5.

Growing up the transformed plant following the transformation event is an obvious step required to allow the plant time to reach maturity thus maximizing the recovery of starch or oil from the plant or plant seed. The skilled artisan would know to grow the plant to maturity to maximize starch and or oil yield.

Applicant traverses that there is no teaching or suggestion in Sowa et al. that an increase in the hemoglobin level would lead to an increased starch and/or oil content in the plants.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Moreover, this is not persuasive because the method of Harper in view of Nykiforuk and further in view of Sowa would lead to

an increase in starch and or oil because said method uses the same gene and the same plant and thus necessarily achieves the same result.

Applicant traverses that absent the hindsight afforded by a reading of Applicants' disclosure, there was no teaching, suggestion, or motivation in the cited references, alone or in combination, to produce starch and/or oil from transformed plants that express at least one hemoglobin.

This is not persuasive for the reasons set forth above.

Remarks

11. No Claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brendan O. Baggot whose telephone number is 571/272-5265. The examiner can normally be reached on Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on 571/272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

bob

ANNE MARIE GRUNBERG
SUPERVISORY PATENT EXAMINER